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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/828,986	04/20/2004	Michael T. Barrett	10031482-1	7617
22878 7590 08/30/2007 AGILENT TECHNOLOGIES INC. INTELLECTUAL PROPERTY ADMINISTRATION, LEGAL DEPT. MS BLDG. E P.O. BOX 7599 LOVELAND, CO 80537			EXAMINER SHAW, AMANDA MARIE	
			ART UNIT 1634	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	Application No. 10/828,986	Applicant(s) BARRETT ET AL.	
	Examiner Amanda M. Shaw	Art Unit 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 08 June 2007.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-31 and 34 is/are pending in the application.
- 4a) Of the above claim(s) 7-24, 30 and 31 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6, 25-29, and 34 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 4/20/2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)  | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date <u>6/8/2007</u> . | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 8, 2007 has been entered.

Claims 1-31 and 34 are currently pending. Claims 7-24 and 30-31 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim.

Claims 1 and 2 have been amended. Claims 1-6, 25-29, and 34 will be addressed herein.

### **Withdrawn Rejections**

2. The rejection made under 35 USC 112 1<sup>st</sup> paragraph (new matter) in section 3 of the Office Action of February 8, 2007 is withdrawn in view of Applicants arguments.

The rejection made under 35 USC 112 2<sup>nd</sup> paragraph over the phrase "A CpG unstructured nucleic acid oligonucleotide containing at least one UNA nucleotide which hybridizes..." in section 4 of the Office Action of February 8, 2007 is withdrawn in view of Applicants arguments. Additionally the rejection made under 35 USC 112 2<sup>nd</sup>

paragraph over the phrase "stringent hybridization" in section 4 of the Office Action of February 8, 2007 is withdrawn in view of Applicants amendments.

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a new rejection:

4. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang (US Patent 6605432 Filed 2000) in view of Yakhini (EP 1288313 Published 3/2003).

Regarding Claim 1 Huang teaches an array comprising CpG dinucleotide rich probes. These CpG dinucleotide rich probes affixed to the solid support of the screening array are employed to identify the presence or absence of methylated sites (Column 7, lines 8-51). Huang also teaches stringent assay conditions. Specifically Huang teaches hybridization was carried out overnight at 65 °C in 10 ml of high efficiency hybridization solution. Washing was preformed once for 20 min in 0.1% SDS-0.5xSSC and twice for 20 min each in 0.1% SDS-0.2xSSC at 65° to 75° C (Column 19 lines 43-50).

Huang does not teach that the CpG probes contain at least one unstructured nucleic acid.

However Yakhini teaches an array of probes comprising unstructured nucleotides. Yakhini further teaches that these probes have a reduced ability to hybridize to each other as compared to nucleic acid probes with naturally occurring nucleotides (Para 0014).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the array of probes taught by Huang by changing the probes of Huang so that the modified probes contain at least one unstructured nucleic acid as suggested by Yakhini. The probes of Yakhini allow for the reduction of cross hybridization between the probes on the array. This is beneficial because cross hybridization can lead to false signals and reduce the number of probes on the array available to bind to the target (Para 0014). Thus modifying the probes of Huang would have allowed for a more effective means for detecting CpG sites.

Regarding Claim 2 Huang further teaches a method wherein the CpG probe binds to an uncleaved CpG island but not to a CpG island cleaved by a methylation sensitive restriction enzyme. Specifically Huang teaches subjecting a nucleic acid sample to a methylation sensitive restriction enzyme which digests unmethylated CpG sites leaving methylated CpG sites in tact, amplifying the methylated CpG fragments, and hybridizing the amplicons to the CpG probe array. Amplicons which are complementary to the probe sequences on the CpG array will produce a positive hybridization signal (column 14, lines 8-67).

Regarding claims 3 and 4 Huang does not teach a method wherein the UNA comprises nucleotides G' and C' wherein G' and C' base pair with each other with a stability that is lower than that of G and C. Further Huang does not teach a method wherein the UNA comprises nucleotides A' and T' wherein A' and T' base pair with each other with a stability that is lower than that of A and T.

However the UNA probes of Yakhini have a reduced ability to form stable hydrogen bonded with base pair (Para 0027). Thus Yakhini teach a method wherein the UNA comprises nucleotides G' and C' wherein G' and C' base pair with each other with a stability that is lower than that of G and C. Further Huang does not teach a method wherein the UNA comprises nucleotides A' and T' wherein A' and T' base pair with each other with a stability that is lower than that of A and T.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the array of probes taught by Huang by changing the probes of Huang so that the modified probes contain at least one

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unstructured nucleic acid as suggested by Yakhini. The probes of Yakhini allow for the reduction of cross hybridization between the probes on the array. This is beneficial because cross hybridization can lead to false signals and reduce the number of probes on the array available to bind to the target (Para 0014). Thus modifying the probes of Huang would have allowed for a more effective means for detecting CpG sites.

Regarding Claim 5 Huang teaches an array of CpG probes (Abstract).

Regarding Claim 6 Huang teaches an array containing at least 1000 different probes (Column 9, lines 61-64).

The following is a new rejection:

5. Claims 25-29 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang (US Patent 6605432 Filed 2000) in view of Yakhini (EP 1288313 Pub 3/2003) and in further view of Ahern (The Scientist 1995).

The teachings of Huang and Yakhini are presented above.

Regarding Claim 25 the combined references do not teach a kit comprising a CpG oligonucleotide.

However, reagent kits for performing hybridization assays were conventional in the field of molecular biology at the time the invention was made. In particular, Ahern discloses the general concept of kits for performing detection methods and teaches that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Ahern (page 22) also teaches that kits provide the benefits of cost-effectiveness

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and time efficiency. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the CpG UNA array and instructions for its use into a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to detect CpG methylation.

Regarding Claim 26 Huang teaches that the probes are attached to an array (Abstract). Therefore Huang teaches a method wherein the oligonucleotide is surface bound.

Regarding Claim 27 Huang teaches that the probes are attached to an array (Abstract). Therefore Huang teaches a method wherein the oligonucleotide is present on an array of features.

Regarding Claim 29 the combined references do not teach that the kit further comprising reagents for labeling the samples. However Huang teaches that the samples are labeled (Column 14, line 42).

However, reagent kits for performing hybridization assays were conventional in the field of molecular biology at the time the invention was made. In particular, Ahern discloses the general concept of kits for performing detection methods and teaches that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Ahern (page 22) also teaches that kits provide the benefits of cost-effectiveness and time efficiency. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to included labeling reagents



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in a kit for the expected benefits of convenience and cost-effectiveness for practitioners of the art wishing to detect CpG methylation.

It is further noted that Claims 28 and 34 have been amended to recite particular instructions to include in the kits. Printed matter in kits such as instructions are not given any patentable weight. Please refer to MPEP 2112.02 III.

The following is a previously presented rejection:

6. Claims 1-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang (US Patent 6605432 Filed 2000) in view of Kuttyavin et al (US Patent 5912340 Issued 1999).

Regarding Claims 1-6 Huang teaches an array comprising CpG dinucleotide rich probes. These CpG dinucleotide rich probes affixed to the solid support of the screening array are employed to identify the presence or absence of methylated sites (Column 7, lines 8-51). Huang further teaches a method comprising: subjecting a nucleic acid sample to a methylation sensitive restriction enzyme which digests unmethylated CpG sites leaving methylated CpG sites in tact, amplifying the methylated CpG fragments, and hybridizing the amplicons to the CpG probe array. Amplicons which are complementary to the probe sequences on the CpG array will produce a positive hybridization signal (column 14, lines 8-67).

Huang does not teach that the CpG probes contain at least one unstructured nucleic acid.

However Kutyaev et al teach probes which contain unstructured nucleic acids (Abstract and Table 2). Specifically Kutyaev et al teach probes which comprise nucleotides G' (6-oxo-purine (hypoxanthine)), C' (pyrrolo-[2,3-d]pyrimidine-2(3H), A' (2-aminoadenine) and T' (2-thiothymine). The modified bases are capable of forming a stable base pair with their natural base partner, but are unable to form a stable base pair with their modified base partner (Abstract, Columns 6-8). Thus Kutyaev et al teach that G' and C' and A' and T' base pair with each other at a stability that is lower than that of G and C and A and T.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the array of probes taught by Huang by changing the probes of Huang so that the modified probes contain at least one unstructured nucleic acid as suggested by Kutyaev et al. The probes of Kutyaev allow for the reduction of the formation of secondary structures between adjacent probes which can interfere with the hybridization between the probe and the target. Thereby modifying the probes of Huang would have allowed for a more effective means for detecting CpG sites.

The following is a previously presented rejection:

7. Claims 25-29 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Huang (US Patent 6605432 Filed 2000) in view of Kutyaev et al (US Patent 5912340 Issued 1999) and in further view of Ahern (The Scientist 1995).

The teachings of Huang and Kutyaev et al are presented above.

Regarding Claims 25-29 and 34 the combined references teach an array comprising CpG UNA probes. Further Huang teaches a method comprising contacting sample nucleic acid with a methylation sensitive restriction enzyme to produce a target composition and assessing the binding of said target to the probe array (Column 14, lines 8-66). Additionally Huang further teaches a method comprising contacting a control nucleic acid (derived from a non cancer cell) and a test nucleic acid (derived from a cancer cell) with a methylation sensitive restriction enzyme to produce a first and second set of target compositions, contacting the first set of target compositions to a first array, contacting the second set of target compositions to a second array, and comparing the binding between both sets (column 16, lines 53-58).

However the combined references do not teach packaging the CpG UNA array and instructions for its use into a kit. However, reagent kits for performing hybridization assays were conventional in the field of molecular biology at the time the invention was made. In particular, Ahern discloses the general concept of kits for performing detection methods and teaches that kits provide the advantage of pre-assembling the specific reagents required to perform an assay and ensure the quality and compatibility of the reagents to be used in the assay. Ahern (page 22) also teaches that kits provide the benefits of cost-effectiveness and time efficiency. Accordingly, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have packaged the CpG UNA array and instructions for its use into a kit for the expected benefits of convenience and cost-effectiveness for practioners of the art wishing to detect CpG methylation.

Additionally it is noted that claims 28 and 34 have been amended to recite particular instructions to include in the kits. Printed matter in kits such as instructions are not given any patentable weight. Please refer to MPEP 2112.02 III.

### ***Response To Arguments***

8. In the response filed June 8, 2007, Applicants traversed the rejection of Claims 1-6 under 35 USC 103(a) as being obvious over Huang in view of Kutyaivin. The Applicants main argument is that Huang provides no problem that one of skill in the art would be motivated to cure using UNA nucleotides since Huang does not mention any problems with his array. As such there is no suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. This argument has been fully considered but is not persuasive. It is noted for the record that KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision *Ex parte Smith*, -- USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (<http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>). In the instant case one of skill in the art would have been motivated to combine these teachings because the probes of Kutyaivin allow for the reduction of the formation of secondary structures between adjacent probes which can interfere with the hybridization between the probe and the target. Thereby modifying the probes of Huang would have allowed for a more effective means for detecting CpG sites. The

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Applicants further argue that Huang relies on PCR methods for amplifying the genome sample thus there would be no need in increase hybridization efficiency. However there is no support for this assertion made by the Applicants. Further the Applicants argue that Huang requires probes that are very long and PCR generated. Since Huangs probes are enzymatically generated they cannot be synthesized using UNA nucleotides. While the probes of Huang were PCR generated it does not mean that the method of Huang could not be modified so that the probes were chemically synthesized instead. Methods of chemically synthesizing probes are well known in the art. It is further noted that how the probes of Huang are made is irrelevant especially since the claims do not require the probes to be made a certain way. For these reasons the rejections made over Huang in view of Kutayavin are maintained.

In the response filed June 8, 2007, Applicants also traversed the rejection of Claims 25-29 and 34 under 35 USC 103(a) as being obvious over Huang in view of Kutayavin and in further view of Ahern. The Applicants main argument is that Ahern fails to meet the deficiencies of Huang and Kutayavin. The examiner disagrees for the reasons presented above. The only limitation that is not taught by the combined teachings of Huang and Kutayavin is packaging the CpG UNA array and instructions for its use into a kit. However Ahern teaches why it would be obvious to do this. For these reasons the rejections made over Huang in view of Kutayavin and in further view of Ahern are maintained.

### ***Conclusion***


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9. No Claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda M. Shaw whose telephone number is (571) 272-8668. The examiner can normally be reached on Mon-Fri 7:30 TO 4:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Amanda M. Shaw  
Examiner  
Art Unit 1634

  
BJ FORMAN, PH.D.  
PRIMARY EXAMINER